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Current topic

Copper deficiency and non-accidental injury

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When parents are brought before the courts accused of causing their children serious injury it is imperative that a strictly medical cause for the injuries should not be overlooked. Unfortunately the adversarial nature of court proceedings often leads those involved, quite understandably, to give a higher priority to winning the case than to discovering the truth. However in child care proceedings finding the truth is often more important than winning the case as it is as much a disaster for a child to be wrongly removed from the care of loving parents as it is to return a child to guilty parents who might further injure or kill him.

In recent years it has been increasingly common to hear the defence that the child's injuries were the result of copper deficiency. As copper deficiency does cause bone disease and may present in the first two years with fractures it is essential that the diagnosis is considered and the appropriate tests are performed at the time that the child first presents with his or her injuries. If this is done, then a case of copper deficiency is not likely to be missed, and a defence of copper deficiency will not prevail merely for lack of evidence to the contrary. The purpose of this paper is to draw attention to the existence of copper deficiency in infants and to review what is known about it, so that the diagnosis will not be overlooked.

Biochemical background[1]

In 1928 Hart *et al*[2] in an elegant series of experiments[3] demonstrated that copper was essential for erythropoiesis in the rat. It is now known that copper is a component of several enzymes, including cytochrome C oxidase, superoxide dismutase, caeruloplasmin, tyrosinase, lysyl oxidase, and dopamine β hydroxylase. These enzymes generally bind between 1 and 8 g atoms of copper per mole, and the presence of copper is essential for their activity. Many of them engage in oxidation reduction reactions.

UNITS OF MEASUREMENT

Because most of the papers quoted in this review did not use SI units, it has been decided to give the values as reported in the original papers. The atomic weight of copper is 63·5, so 1·0 μg copper/dl=0·157 mmol/l. Because the molecular weight of caeruloplasmin is not known precisely the best SI unit of concentration is g/l.

Copper deficiency

The features of copper deficiency given below are based on 52 cases reported in the paediatric literature since 1956.[5–27] The reports vary considerably in the amount of detail given, depending on the extent of knowledge at the time they were written, the diagnostic facilities available, the analytical methods used, and the purpose of the report (that is, mainly radiological, mainly biochemical, or mainly clinical). Nevertheless though the amount of data given are variable, and in some cases are possibly open to other interpretations, there is no conflict between any of the reports, which makes it probable that they are all describing, in different ways, the same condition. For this reason I have included all cases where there are sufficient data to analyse.

The characteristics of copper deficiency in infants are summarised below.

SYNDROME OF COPPER DEFICIENCY IN INFANTS

- Psychomotor retardation.
- Hypotonia.
- Hypopigmentation.
- Prominent scalp veins in palpable periosteal depressions.
- Radiological changes of osteoporosis, blurring and cupping of the metaphyses, sickle shaped metaphyseal spur formation, subperiosteal new bone formation, and fractures.
- Pallor.
- Sideroblastic anaemia, resistant to iron

treatment. Bone marrow shows vacuolated erythroid and myeloid cells with iron deposition in the vacuoles.
- Hepatosplenomegaly (a feature of sideroblastic anaemia).
- Neutropenia, usually $<1{\cdot}0\times10^9$/l.
- Plasma copper concentration usually <40 μg/dl, and caeruloplasmin <13 mg/dl.

Many of the features can be explained on the basis of deficiency of particular copper enzymes. The prominent scalp veins and bone changes are thought to result from impaired collagen and elastin cross linking due to depressed lysyl oxidase activity. The consequent reduction in strength of the bone collagen causes fragile bones that fracture easily. The hypopigmentation is probably due to depressed tyrosinase activity and impaired melanin synthesis. The sideroblastic anaemia is less well understood, but there seems to be depression of iron transport into the mitochondria, and impaired incorporation of iron into protoporphyrin IX within the mitochondria.[3] The cause of the neutropenia is not understood.

Diagnosis of copper deficiency

If it is thought that fractures and changes in the growing ends of long bones may be due to copper deficiency, the diagnosis cannot be established for certain without quite detailed investigations, and these are often lacking in cases where non-accidental injury is suspected. However consideration of what is known about copper deficiency will certainly indicate if the diagnosis is at all probable. Of the 52 cases reported below, 51 were under 5 years of age,[5 6 8–27] and 49 were 18 months or less at the time of diagnosis.[5 6 8–10 12–27] Those classed as full term include seven infants who are presumed to be full term but whose birth weight or gestation are not given. The low birthweight infants are infants whose birth weight is given or who are stated to be of low birth weight (<2500 g). Their median birth weight was 1040 g (range 680–2300 g).

Prediposing factors

In the published reports one or more of a number of predisposing factors have been present in every case. These are listed below.

(1) LOW BIRTH WEIGHT

Forty per cent of reported cases were less than 2500 g at birth.[5 6 9 10 13 21 22 24 25 27] Low birthweight infants have lower body stores of copper at birth than full term infants (3·5 mg/kg fat free body weight at 20 weeks' gestation rising to 4·8 mg/kg fat free body weight at term).[28] During the last three months of gestation they accumulate copper at a rate of about 51 μg/kg/day.[29] If, however, they are born prematurely they will be in negative copper balance for up to six weeks after birth.[30] Full term infants also have a period of negative balance after birth.[31] Though this will cause a transient decline in the total body copper it is not thought to cause copper deficiency if the subsequent dietary copper intake is sufficient. The full term infant at least has a high concentration of copper in the liver[32 33] and the current evidence suggests that full term infants have stores sufficient for at least five months and low birthweight infants for at least two months.

Causes of bone mineral deficiency in low birthweight infants

The smaller low birthweight infants invariably experience a decline in the concentration of bone mineral after birth when compared with a fetus of equivalent gestation *in utero*. This occurs because they cannot absorb and retain the amount of calcium and phosphorus that would be laid down had they remained *in utero*.[34] If they are fed breast milk there is an absolute dietary deficiency of calcium as on maximum intake they would receive only about half the intrauterine accumulation rate. Because there is insufficient phosphorus in breast milk low birthweight infants fed breast milk tend also to develop phosphate deficiency rickets,[35] unless they are given phosphate supplements. They therefore develop weak bones and are prone to fractures of ribs and long bones even if they do not have copper deficiency. They do not, however, develop skull fractures.

(2) DIETARY DEFICIENCY OF COPPER

Total parenteral nutrition

Twenty three per cent of the infants received total parenteral nutrition.[6 8 15 16 17 19 24 26] In eight of the cases the solutions were deficient in copper. In the three other cases copper had been added to the solution,[24] but other predisposing causes—namely, prematurity and copper deficient milk—were present.

Copper deficient milk

Fifty four per cent of infants were fed exclusively cows' milk or predominantly cows' milk with very short periods of breast feeding.[6 10 11 14 18 21 23] A further 12% were fed formula milks[5 9 12 13 27] of which at least one was copper deficient.[5] The changes in the concentration of copper in breast milk are given in tables 1 and 2. Cows' milk has a much lower concentration of copper in it than breast

Table 1 *Changes in concentration of copper in human milk during lactation*[36 37]

Time postpartum	*Copper concentration*	
	μg/dl	*(SD)*
2–5 days	46	(18)
6–13 days	67	(19)
15–28 days	58	(8)
2 Months	61	(16)
3 Months	42	(22)
4–7 Months	29	(23)

Table 2 *Comparison of changes in copper concentration in milk from mothers of full term and preterm infants*[38]

Time postpartum	*Copper concentration μg/dl (SD)*	
	Full term infants	*Low birthweight infants*
3–5 Days	72 (13)	83 (21)
8–10 Days	73 (21)	78 (18)
12–17 Days	57 (8)	75 (24)
28–30 Days	58 (9)	63 (14)

milk. The copper content of cows' milk is stated to be 20 μg/dl range 10–30 μg/dl[39] and in one report values as low as 5·7 μg/dl were found.[21] Copper deficiency has never been described in an infant fed exclusively on breast milk, or a full term infant fed a formula known to contain adequate amounts of copper that is, >40 μg/dl.

(3) ANTECEDENT MALNUTRITION

Twenty five per cent of the cases suffered from severe antecedent malnutrition. This was due to a starvation diet[10] or malabsorption and diarrhoea,[8 25] giardiasis,[10] a probable diasaccharidase deficiency,[11] short bowel,[16 19 26] or coeliac disease.[12] Vomiting was reported in 13% of cases and probably contributed to the aetiology of the malnutrition.[6 10 11 18 23]

(4) PERITONEAL DIALYSIS

There is one report of a 16 year old with cystinosis who developed copper deficiency after several years of ambulatory peritoneal dialysis.[7]

Clinical features

(1) AGE AT PRESENTATION (Infants <18 months at diagnosis)

The median age at presentation for full term infants[7 8 10–12 14–21 23 26] was 8·3 (range 5–18) months and for the low birthweight infants was 3·0 (range 2·2–15) months.[5 6 9 10 13 21–25 27] This difference presumably reflects the difference in the body stores of copper present at birth.

(2) HISTORY AND PHYSICAL EXAMINATION

Details of physical examination were reported in only 14 of the 52 cases.[5 6 10 12 14 18 20 24 25] In these 14 infants hypotonia was reported in 43% (lax joints in one case), hypopigmentation in 29%, psychomotor retardation in 21%, skin rash in 21%, dilated veins in 15%, and hepatosplenomegaly in 15%. There was no mention of bruising or of blue sclerae in any of the 52 cases, and no case had cerebral haemorrhage. In no case was there any evidence of copper deficiency in the mother during pregnancy, and there was no case where there was any family history of copper deficiency.

(3) INFECTION

Specific infections are mentioned in six cases. They include two cases of congenital syphilis and tuberculosis,[10] one case of bronchopneumonia,[27] one case of infected central venous catheter used for total parenteral nutrition,[16] one of otitis media,[18] and the case of giardiasis mentioned above.[10] Others are described as 'mild and non specific'.[21] These cannot easily be construed as being a consequence of copper deficiency and the giardiasis probably contributed to it.

Plasma copper and caeruloplasmin

In the full term infants the median plasma copper was 37 μg/dl (range 7–89), and the median caeruloplasmin was 3·0 mg/dl (range 0·4–13·0). In the low birthweight infants the median plasma copper was 28 μg/dl and the median caeruloplasmin was 3·0 mg/dl (range 0·0–4·0). During the last 30 years the analytical methods have improved, and most of the higher values in the literature date from the earlier period 1956–70. In the more recent reports where modern methods (that is, atomic absorption spectrophotometry) were used no case of copper deficiency has been reported in a full term infant with a plasma copper of more than 43 μg/dl and in a low birthweight infant with a plasma copper of more than 33 μg/dl.

PLASMA COPPER AND FRACTURES

The median plasma copper concentration in those infants who had fractures (see below) was 14·5 μg/dl (range 4·5–68). Only one value was over 33 μg/dl and this dated from 1964 when analytical methods were not so reliable.

NORMAL PLASMA COPPER

The plasma copper concentration in pregnant and

non-pregnant women and changes in plasma copper in full term infants and preterm infants are given in tables 3, 4, and 5. In evaluating the plasma copper it is important to take into account the birth weight and the age of the baby as the plasma copper and caeruloplasmin both vary with postnatal age and gestation. In the newborn about 85% of the plasma copper is bound to caeruloplasmin and the remainder is probably bound to the serum albumin and complexed with aminoacids. The plasma copper and caeruloplasmin are both low at birth and rise to adult values at about 6 months of age (table 3). The plasma concentrations in low birthweight infants are about the same as full term infants at birth but rise more slowly (table 4). The values shown in table 4 were the same whether the infants were fed a formula containing 40 μg/dl of copper or one containing 167 μg/dl of copper.[46] It therefore seems likely that these values are representative of plasma copper concentrations to be found in low birthweight infants who are not copper deficient. The normal range would therefore be the mean (2 SD). From these data it can be seen that a small preterm infant of 2–3 months may have a very much lower plasma copper concentration than a full term infant of same postnatal age and yet not have copper deficiency.

Table 3 *Changes in serum copper with age in full term infants*[40 41 42]

Postnatal age	*Plasma copper concentration*	
	μg/dl	*(SD)*
Cord blood	29	(11)
5 Days	47	(9)
1 Month	63	(17)
3 Months	81	(17)
5 Months	104	(25)
6–12 Months	111	(19)
6–12 Years	109	(17)

Table 4 *Changes in plasma copper in preterm infants*[43]

Postconceptional age (weeks)	*Plasma copper concentration*	
	μg/dl	*(SD)*
25–28	29	(17)
29–30	27	(15)
31–32	32	(18)
33–34	36	(15)
35–36	39	(14)
37–38	47	(24)
39–40	53	(12)
41–42	60	(12)
43–44	70	(28)
45–46	65	(16)
47–48	82	(18)

Table 5 *Copper and caeruloplasmin concentrations in maternal and fetal blood*[40 44 45]

	Copper concentration		*Caeruloplasmin concentration*	
	μg/dl	*(SD)*	*mg/dl*	*(SD)*
Male: plasma	92	(12)	31	(4)
Female: plasma (non-pregnant)	107	(23)	31	(5)
Female: plasma (on oral contraceptives)	221	(62)	57	(21)
Pregnant: plasma taken at 16 weeks	162	(27)	71	(24)
Pregnant: plasma taken at 36 weeks	192	(24)		
Pregnant: serum taken at term	221	(54)	91	(13)
Cord blood: serum taken at term	29	(11)	10	(6)

Haematological changes

ANAEMIA

Ninety two per cent of the full term infants and 85% of the low birthweight infants had a haemoglobin concentration of less than 100 g/l. The median haemoglobin of the full term infants was 49 g/l (range 26–136) and of the low birthweight infants was 70 g/l (range 27–119). Examination of the bone marrow showed typically maturation arrest with marked vacuolisation in the erythroid and myeloid cells with numerous ringed sideroblasts.[5] The picture is not therefore one of iron deficiency though in some cases, notably those fed cows' milk, the

Table 6 *Bone changes reported in copper deficiency**

	No (%) Full term infants	*No (%) Low birth weight infants*
Fractures	*(n=31)*	*(n=20)*
Fracture of long bone(s)	3 (10)	5 (25)
Fracture of epiphyseal plate(s)	2 (6)	2 (10)
Fracture of ribs	—	3 (15)
Metaphysial chip fracture	1 (3)	—
Fracture of the skull	—	—
Other changes	*(n=14)*	*(n=13)*
Osteoporosis	8 (57)	11 (85)
Fraying and cupping of the metaphyses	9 (64)	11 (85)
Spurs	8 (57)	—
Subperiosteal new bone formation	6 (43)	7 (54)

*The incidence of fractures is for the whole group, and the incidence of other changes is for the group in whom the results of *x* rays were reported. Note that some infants had more than one fracture.

reticulocyte response to iron treatment showed that iron deficiency did coexist with the copper deficiency. The median plasma iron concentration in the full term infants was 20 μg/dl (range 4–114) and in the low birthweight infants was 16 μg/dl (range 10–78). The higher median haemoglobin concentration in the low birthweight infants was probably attributable to the fact that they were transfused.

NEUTROPENIA

A neutropenia of less than $1{\cdot}0\times10^9$/l was found in 84% of the infants in whom the results of a white blood cell count were reported (n=25)[5–7 9 10–16 18 20 24–27] and all these infants had a neutrophil count less than $2{\cdot}0\times10^9$/l. There were no differences between the low birthweight infants and the full term infants. The median neutrophil count was $0{\cdot}376\times10^9$/l (range 0·049–1·9). As in infants with fractures the median neutrophil count (n=9) was $0{\cdot}393\times10^9$/l (range 0·08–1·2) it is doubtful if the diagnosis of copper deficiency of sufficient severity to cause fractures should be considered in the absence of neutropenia.

Bone disease

The results of *x* ray examination of the bones of infants with copper deficiency are summarised in table 6. Fractures were found in 11 cases.[5 9 10 11 13 14 17 19 25 27] The percentage incidence of fractures is based on the whole group of infants (n=51) on the supposition that a fracture is unlikely to be missed clinically. The percentage incidence of the other changes are based only on the cases where bone changes on *x* ray are reported (n=27)[5 6 8–11 13–20 24–27] because many of the findings are not evident clinically and might not be detected if an *x* ray film was not taken. The subperiosteal new bone formation can be very extensive and reflect organising subperiosteal haemorrhage,[17 19 25] in other cases it can be quite inconspicuous, and may simply reflect normal bone growth, particularly in premature infants.

DISTINGUISHING BONE CHANGES IN COPPER DEFICIENCY FROM THOSE IN NON-ACCIDENTAL INJURY

The most important thing to keep in mind is that both a fracture and a subperiosteal haemorrhage are evidence that a force has been applied to a bone, but unless the magnitude of the force is known (and this is sometimes in dispute), their presence gives no information as to the strength of the bone, so they cannot be used as evidence for the presence or absence of copper deficiency. They are neutral in that respect. Evidence for the presence of bone disease must be sought elsewhere.

Low birthweight infants, because they have small slender bones and experience difficulty in absorbing and retaining bone mineral at a rate that is comparable with the *in utero* accumulation rate, have a higher incidence of osteoporosis and fractures than full term infants even in the absence of copper deficiency.

The features that should alert one to the diagnosis of copper deficiency are the cupping and fraying of the metaphysis of the long bones, and the sickle shaped metaphyseal spurs, which sometimes fracture, and seem to be very characteristic of copper deficiency. The best photographs of these appearances are to be found in the paper by Grünebaum *et al.*[14] As copper deficiency is a metabolic bone disease it will affect the entire skeleton in a symmetrical manner, being particularly evident in the most rapidly growing bone ends, namely the wrists and the knees. The proximal ends of the femora and humeri are also affected as are the costochondral junctions, which may enlarge. The bone age seems frequently to be retarded.[14] The findings on *x* ray examination may be confused with those of scurvy or rickets but the help of an experienced radiologist and the characteristic biochemistry and haematology should make the diagnosis fairly straight forward. The age at diagnosis in full term infants with fractures ranged from 6·5 to 60 months (median 9 months) whereas the age at diagnosis in the low birthweight infants with fractures ranged from 2·2 to 7·0 months (median 2·8 months). Therefore when a full term infant of less than 6·5 months or a preterm infant of less than 2·2 months presents with fractures copper deficiency is not a likely diagnosis. It is noteworthy that skull fractures have never been reported in copper deficiency and neither have rib fractures in full term infants with copper deficiency. Fractures have never been reported as a late sequel to copper deficiency.

In contrast the bone changes in non-accidental injury are usually unsymmetrical and where they are numerous they are often of different stages of healing indicating that they are injuries that have taken place over a period of time. Though individually a metaphyseal chip fracture or subperiosteal haemorrhage may resemble those seen in copper deficiency, they occur against a background of an otherwise radiologically normal skeleton, without any retardation of the bone age.

Response to treatment

In the reported cases the median copper intake used in treatment was 290 μg copper/kg/day (range 63–800) and in one case on total parenteral nutrition, intravenous treatment was given in a dose of 50

μg/kg/day. Treatment resulted in a reticulocyte response within 1–2 weeks, median 4·6% (range 2–14%), and the neutrophils rose above $1{\cdot}0\times10^9$/l within about five days. Healing of the fractures and resolution of the other bone changes were well advanced after 30 days. As some of the infants recovered without any special treatment other than introducing a more varied diet with a higher copper content, it is possible that the occasional infant may pass through a period of transient deficiency and recover spontaneously as his repertoire of food increases, without ever being diagnosed.

Genetic diseases of copper metabolism

Though there are a number of diseases of copper metabolism described in experimental animals there are only two that have been established with certainty in man, Menkes' disease, and Wilson's disease. The only one to be confused with copper deficiency is Menkes' disease.[47] This is an X linked recessive condition that only occurs in boys. Though it has many of the features of dietary copper deficiency including the low plasma copper and caeruloplasmin, and the bone changes, anaemia and neutropenia do not occur. Intracranial haemorrhages do occur in patients with Menkes' disease but have never been reported in dietary copper deficiency in infants. The presence of convulsions and hypothermia and the relentless downhill course with death usually within two years makes confusion unlikely. A syndrome of benign familial copper deficiency has been described in a single family.[48] The propositus at 21 months of age had fair hair, a seborrhoeic rash on his face, convulsions, and bone changes resembling those of copper deficiency. There were no fractures and no features suggestive of non-accidental injury. The plasma copper was low but the caeruloplasmin concentration was normal.[49] The fits and the rash responded to treatment with copper.

Adult copper deficiency

This has not to my knowledge been described in a pregnant woman and the cases in the literature have been found in patients on total parenteral nutrition with inadequate concentrations of copper in the solutions, and in patients with bowel resections.[50 51]

Copper content of milks

There is some uncertainty about the copper content of formulas sold for infant feeding in the United Kingdom and Europe. Table 7 gives the mean values and range of copper found in formulas in different countries. The data are mainly from Lönnerdal *et al*[52] but the data on English milks are my own unpublished data from 1982. It can be seen that some formulas have a very low copper content and at 150 ml/kg/day would supply much less than the amount supplied by breast milk (table 1 and 2) or the recommended requirements for full term infants (see summary below). If copper is to be added to infant formulas in manufacture then the milk powder must be packed under nitrogen to prevent oxidation of the fatty acids, which turns the milk rancid. Today most milks are packed in this way.

Table 7 *Copper concentration of different infant formulas*

Country of origin	*No of samples*	*Copper concentration μg/dl*	
		Mean	*Range*
United States of America*	14	48	31–65
Sweden*	12	18	3–70
West Germany*	12	20	1–135
Japan*	8	6	2–15
The Netherlands*	2	28	14–43
United Kingdom*	2	14	5–23
Fullterm formula†	9	18	1–47
Preterm†	3	68	62–73
Soy formula†	1	51	
France*	2	12	5–20
Norway*	1	25	

*Reference 52; †JCL Shaw, unpublished data: analyses performed in 1982.

Recommendations of various bodies

(1) EUROPEAN SOCIETY FOR PAEDIATRIC GASTROENTEROLOGY AND NUTRITION (ESPGAN) COMMITTEE ON NUTRITION (1977)[53] (Full term infants)

Minimum value 30 μg/100 kcal (20 μg/100 ml).

(2) DEPARTMENT OF HEALTH AND SOCIAL SECURITY (DHSS) (1980)[54] (Full term infants)

'It seems likely that the amount of copper in infant feeds should be not more and not less than the amounts present on average in mature human and cows' milk, that is to say not less than 10 μg and not more than 60 μg/100 ml, but at present sufficient information is not available for a recommendation to be made'.

(3) AMERICAN ACADEMY OF PEDIATRICS (1976)[55] (Full term infants)

Minimum intake 90 μg/100 kcal.

(4) AMERICAN ACADEMY OF PEDIATRICS (1977)[56] (Low birth weight infants)

'Recent data suggests that an intake of 90 μg/100 kcal is desirable'.

(5) CANADIAN PAEDIATRIC SOCIETY: (1981)[57]
'It has been suggested that low birthweight infants require 90 μg/100 kcal to avoid copper depletion'.

(6) AMERICAN ACADEMY OF PEDIATRICS (1985)[58] (Low birth weight infants)
'90 μg/100 kcal continues to be appropriate'.

Unfortunately the recommendations of the DHSS (see above) were framed in such a way that the manufacturers felt that they did not necessarily have to fortify formulas with copper. As a result the copper content of some infant formulas sold in the United Kingdom in the past was less than 10 μg/dl,[59] and in some samples of milk copper was almost undetectable (JCL Shaw, unpublished data). However at the present time SMA, Cow and Gate Premium, and Farley Health Product Milks (Osterfeed, Ostermilk Complete, and Ostermilk II) all contain enough copper (roughly 40 μg/dl), and have done since at least 1983. The Milupa products on the other hand contain more variable amounts of copper. The manufacturers claim that Aptamil contains 46 μg/dl, Milumil 26·2 μg/dl, and Preaptamil, the formula designed for preterm infants, only 10 μg/dl.

It is therefore evident that while most milks used for infant feeding in the United Kingdom contain what is believed to be sufficient copper some do not. The most striking example is Preaptamil and this milk is soon to be replaced by a milk with a higher copper content. Unless circumstances have changed since the report of Lönnerdal *et al*[52] there may also still be milks marketed on the continent of Europe that contain insufficient copper.

Copper deficiency and non-accidental injury

Copper deficiency should be considered in the differential diagnosis of bone fractures in young infants. Once copper deficiency has been proposed it cannot be refuted as a cause with complete certainty unless there are detailed radiographs of the whole skeleton, measurements of plasma copper, caeruloplasmin, haemoglobin and differential white cell count, and possibly bone marrow. The presence of a predisposing cause, the characteristic age at onset, and a response to treatment add to the security of the diagnosis. However it is possible, in the absence of specific diagnostic tests, to determine the probability that a correct diagnosis has been made.

If the patient is a full term infant, under 5 months of age, who has been breast fed, or has received a milk with a copper concentration of 40 μg/dl or more then the diagnosis is unlikely. Such a case has never been described. The absence of the predisposing conditions mentioned above (prematurity, preceding malnutrition, a deficient copper intake, malabsorption) make the diagnosis even more unlikely. If the copper deficiency is sufficiently severe to cause fractures then some of the other clinical features (for example, skin rash, hypotonia, psychomotor retardation, or hypopigmentation) are likely to be present, together with anaemia, neutropenia, and a low plasma copper concentration.

Neither skull fractures nor cerebral haemorrhage have ever been described in infants with copper deficiency, and rib fractures have never been described in full term infants with copper deficiency. The presence of any of these points to another diagnosis. The demonstration of normal bones, and in particular wrists and knees, makes the diagnosis very unlikely. Obviously if the other features of copper deficiency (hypocupraemia, low caeruloplasmin, neutropenia, and sideroblastic anaemia) are absent then the diagnosis can be confidently ruled out.

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